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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/595,151 | 03/07/2006 | Kelly Renee Bales | X-16212 | 3398 |

25885 7590 01/25/2008

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| EXAMINER | |
|---|---|
| MARVICH, MARIA | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1633 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 01/25/2008 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@lilly.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/595,151 | BALES ET AL. | |
| | Examiner | Art Unit | |
| | Maria B. Marvich, PhD | 1633 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *07 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/7/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

Claims 1-36 are pending.

### *Claim Rejections - 35 USC § 112, first paragraph*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reducing brain burden of amyloid beta in a mouse model by administration of lentivirus comprising the coding sequence for apoE2, does not reasonably provide enablement for any other embodiment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

The instant claims are drawn to a method of 1) inhibiting a condition or disease associated with Aβ (claims 1-10) 2) reducing progression of inhibiting a condition or

disease associated with Aβ (claims 11-26) and 3) preventing or reducing brain Aβ burden (claims 27-36). The specification teaches development of a lentivirus expressing human apoe2 or apoe4. The lentivirus was introduced into PDAPP mice that overexpress a mutated form of human amyloid precursor protein under the control of the PDF promoter to the hippocampus of these mice. Apoe4 expression lead to an increase in brain Aβ burden while apoE2 expression reduced brain burden. However, applicants' claims are broadly drawn to treatment of *any* subject for *any* Aβ disease or condition in order to inhibit it or reduce its progression or prevent or reduce brain burden of Aβ.

The MPEP teaches, "However, claims reading on significant numbers of inoperative embodiments would render claims non-enabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. Atlas Powder Co. v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971). (see MPEP 2164.08(b). In the instant case, the scope of the claimed invention is extremely broad which exacerbates a highly unpredictable art. First, conditions or diseases associated with Aβ are a broad basis of disease for which applicants' disclosure teaches use of a mouse model for Alzheimer's in which a single marker of this disease is reduced. It is highly unpredictable that this mouse model for Alzheimer's' can be extrapolated to a multitude of other diverse conditions. While the specification discloses such conditions can be Alzheimer's, cerebral amyloid angiopathy and Down's as well as mild cognitive impairment, the art teaches that inflammatory muscle disorders are also Aβ disorders (). It is not clear how non-brain based disorders can be treated by administration to the brain as a target site.

This is exacerbated as it is well known in the art that animal models . For example, the PDAPP does not recapitulate the whole etiology of Alzheimer's. Richardson and Burns in reviewing the art of Alzheimer mouse models demonstrates that the model fails to meet all criteria of the neuropathology of human AD as it is absent cortical or hippocampal neuronal loss or neruofibrillary tangles (see table 1 and bridging ¶ page 93-94) and as such it does not reflect a complete picture of AD much less the genus of Aβ conditions or diseases. Furthermore, recent evidence suggests that the fibrils deposited in the brains of mice are distinct from those found in humans (see page 93, col 2, ¶2-3). Hence, the models mimic only aspects of the disease. Kahle et al further this analysis by arguing that the models are nothing like the slow progression of the real diseases in life and treatments that appear successful are only symptomatic with disease rarely abated (see page 126, col 1, ¶ 2).

Applicants own review of their art demonstrates that the differences in mouse and human subjects are an issue with successful application of their claimed invention. "Further experiments were conducted by expressing apoE with lentiviral vectors in PDAPP/ApoE-knockout mice that develop Abeta deposits with aging. Of note, expression of apoE4 led to increased deposition of amyloid in these animals. ApoE2, on the other hand, induced a marked decrease in Abeta accumulation, as shown by immunohistochemistry and enzyme-linked immunosorbent assay (ELISA).ApoE2 thus appeared to have both a protective and therapeutic effect in this animal model. Dr. Paul was, however, quick in adding that he was not advocating for a gene therapy approach of this kind in AD. The lentiviral vectors used, in fact, were toxic for a specific set of

neurons in the hippocampus of treated mice." (citations removed, Mariani, 2004, page 3, ¶1-2). This touches on the unpredictability associated with viral based therapies recently highlighted in the art, see for example, Check, Nature, 2003.

Finally, the claims read on inhibiting a condition or disease associated with Aβ, which requires the ability to predict the subjects that would require treatment. However, the ability to predict for whom the therapies would be required is highly unpredictable. Screening procedures for indications of those requiring inhibition of the onset of disease are unknown and highly prejudicial leading to conditions in which those who require the treatment cannot be distinguished from those who do not. Hence, the instant invention has been assessed completely as it relates to the prior art in light of the guidance provided in the specification, which demonstrates that extrapolating the experimental procedures of the instant disclosure is highly unpredictable. The invention recites use of a broad group of diseases to be treated by administration of apoE2 lentivirus, however, given the unpredictability of the art, the poorly developed state of the art with regard to predicting the functionality of mouse models, the lack of adequate working examples and the lack of guidance provided by applicants, the skilled artisan would have to have conducted undue, unpredictable experimentation to practice the claimed invention.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 5, 6, 11, 12, 15, 16, 22, 23, 26, 27, 28, 31 and 32rejected under 35 U.S.C. 102(e) as being anticipated by Verlinden et al (US 2002017213; see entire documents).

Verlinden et al teaches development of retrovirus derived (i.e. lentivirus) vectors encoding apoe2 for administration to human brains (see e.g. ¶ 27, 15 and abstract) to treat cells with processing of Aβ. Sites such as the hippocampus are preferred targets.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Maria B Marvich, PhD
Examiner
Art Unit 1633